

## REMARKS

### A. Supplemental Response

This Response supplements the Response filed on March 17, 2008.

### B. Claims Status

Claims 21-46 are pending in this Application.

### C. The March 17, 2008 Response

In the March 17, 2008 Response, Applicants presented the March 12, 2008 Declaration of Mr. Akihisa Nakajima to demonstrate that surprising and unexpected results are obtained in the weight percentage of the iodine compound included in the vesicle when employing the method of claim 21.

However, Applicants inadvertently failed to present arguments to specifically distinguish product-by-process claim 27 from the cited art, and inadvertently failed to respond to the § 112 rejection against claim 42.

This Supplemental Response addresses the prior art rejections to claim 27 and the formal rejection to claim 42.

D. The contrast medium of claim 27 is not anticipated by or unpatentable over the cited references

Claims 21-43 had been rejected as being unpatentable over either Otake (U.S. 2004/0099976) or Castor (U.S. 5,554,382) in view of Sachse (*Invest. Radiol.*) and Mackaness (U.S. 4,192,859). Claims 21-42, 44 and 45 had been rejected as being unpatentable over either Otake or Castor in view of Sachse and Klaveness (U.S. 5,676,928). Claim 27 had been rejected as being anticipated by Na (U.S. 5,326,552).

Applicants respectfully submit that the contrast medium of product-by-process claim 27 is not anticipated by or obvious based on the teachings of the cited references.

In the March 17, 2008 Response, Applicants presented the March 12, 2008 Declaration of Mr. Akihisa Nakajima. In the Table attached to the Declaration, it was shown that the weight percentage of the iodine compound included in the vesicle substantially increases when employing the method of claim 21. Thus, it was shown that the contrast medium of claim 27 is different than and superior to the contrast medium of the cited art. Mr. Nakajima declared in section 11 of the Declaration that he finds such results surprising and unexpected. A more detailed analysis follows.

As shown in the Table attached to the Declaration, Sample A was prepared based on the teachings of Mackaness (inclusion of

an iodine compound, without using super or subcritical carbon dioxide). The iodine inclusion percentage was 0.5%.

Sample B was prepared similar to Sample A, except that a pharmaceutically active compound was employed instead of an iodine compound. The active compound inclusion percentage of Sample B was 6%. Thus, by comparing Sample A with Sample B, it was shown that 12x more of the pharmaceutically active compound was included in the vesicles compared to the iodine compound (neither Sample A or Sample B used a super or subcritical carbon dioxide method).

For Samples C and D, the method of Otake was employed (super or subcritical carbon dioxide). In Sample C, 15% of the pharmaceutically active compound was included in the vesicles. Thus, by comparing Sample C with Sample B, it was shown that the method of Otake increased the inclusion percentage from 6% in Sample B to 15% in Sample C, i.e., a 2.5x increase.

Based on the 2.5x inclusion increase for the pharmaceutically active compound achieved by employing the method of Otake in Sample C compared to the method of Mackaness in Sample B, one would expect a similar 2.5x increase for an iodine compound by employing the method of Otake instead of the method of Mackaness. However, as seen by comparing Sample D with Sample A, a 2.5x increase was not achieved. Instead, a 34x increase in the inclusion percentage was achieved using the

method of Otake in combination with an iodine compound as recited in claim 27.

Thus, Mr. Nakajima demonstrated that the claimed invention produces a 34x increase in the inclusion percentage of iodine using the method of Otake, when only a 2.5x increase would be expected. The Declaration therefore demonstrates that the contrast medium of claim 27 is different than and superior to the contrast medium of the cited art.

Applicants respectfully submit that claim 27 is not anticipated by or unpatentable over the cited references taken alone or in combination.

E. Claim 42

The Examiner rejected claim 42 as indefinite stating that the similarity of the concentrations of the iodine compound and the additive is not defined in the specification.

Applicants direct the Examiner to the portion of the application beginning on the final line of page 33 and ending on the second line of page 34. In this section, it is explained that the expression "substantially the same" means that the concentrations are nearly the same. Thus, a definition of the rejected phrase appears in the specification. Moreover, it is noted that those in the art understand that the expression

"substantially the same" means that the concentrations of the iodine compound and the additive do not significantly differ.

Applicants respectfully submit that claim 42 is definite.

F. Conclusion

In view of the foregoing and the enclosed, it is submitted that the Application is in condition for allowance and such action is respectfully requested. Should any further fees or extensions of time be necessary in order to maintain this Application in pending condition, appropriate requests are hereby made and authorization is given to Account #02-2275.

Respectfully submitted,

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